Pyrexia of unknown origin

Dr. Nashwan Mansoor

Pyrexia of unknown origin

❖ **Pyrexia of unknown origin (PUO) :- was classically defined as A temperature above 38.0°C on multiple occasions for more than 3 weeks, without diagnosis, despite initial investigation in hospital for 1 week.**

➢ **The definition has been relaxed to allow for investigation**

❑ **Over 3 days of inpatient care.**

❑ **Three outpatient visits.**

❑ **One week of intensive ambulatory investigation.**

➢ **Up to one-third of cases of PUO remain undiagnosed.**

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❖ Clinical assessment

- Major causes of PUO are illustrated below.
- Rare causes, such as periodic fever syndromes, considered in those with a family history.
- Children and younger adults are more likely to have infectious (viral infections).
- Older adults are more likely to have certain infectious and non-infectious causes.

- Detailed history and examination should be repeated at regular intervals to detect emerging features (e.g. rashes, signs of infective endocarditis or features of vasculitis).
- In men, the prostate should be considered as a potential source of infection.
- Clinicians should be alert to the possibility of factitious fever.

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❖ A etiology of pyrexia of unknown origin (PUO)

❑ Infections (~30%)

➢ Specific locations :-

- Abscesses: hepatobiliary, diverticular, urinary tract, pulmonary, and CNS.
- Infections of oral cavity (including dental), head and neck (including sinuses).
- Bone and joint infections.
- Infective endocarditis.

➢ Specific organisms :-

- TB (particularly extrapulmonary).
- HIV-1 infection.
- Other viral infections: cytomegalovirus (CMV), Epstein–Barr virus (EBV).
- Fungal infections (e.g. Aspergillus spp., Candida spp. or dimorphic fungi).
- Infections with fastidious organisms (e.g. Bartonella spp., Tropheryma whipplei).

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❖ A etiology of pyrexia of unknown origin (PUO)

❑ Infections (~30%)

➢ Specific patient groups

- Geographically restricted infection :-

➢ Malaria, dengue, rickettsial infections, Brucella spp..

➢ Amoebic liver abscess, enteric fevers, Leishmania spp..

➢ Middle East respiratory syndrome coronavirus (MERS-CoV; Arabian Peninsula)

- Residence in or travel to a region with endemic infection:

➢ TB, extensively drug-resistant TB, Brucella spp., HIV-1,Trypanosoma cruzi.

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❑ Infections (~30%)

➢ Specific patient groups

- Nosocomial infections:

➢ Pneumonia.

➢ Infections related to prosthetic materials and surgical procedures.

➢ Urinary tract infections.

➢ Central venous catheter infections.

- HIV-positive individuals: -

➢ Acute retroviral syndrome.

➢ AIDS-defining infections (disseminated Mycobacterium avium complex (DMAC), Pneumocystis jirovecii pneumonia, CMV and others)

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❖ A etiology of pyrexia of unknown origin (PUO)

❑ Malignancy (~20%)

➢ **Hematological malignancy**

- ✓ **Lymphoma.**
- ✓ **Leukemia.**
- ✓ **Myeloma**

➢ **Solid tumors in ;**

- ✓ **Renal.**
- ✓ **Liver.**
- ✓ **Colon.**
- ✓ **Stomach.**
- ✓ **Pancreas.**

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❖ A etiology of pyrexia of unknown origin (PUO)

❑ Connective tissue disorders (~15%)

➢ **Older adults**

- **Temporal arteritis/polymyalgia rheumatica**

➢ **Younger adults**

- **Still’s disease (juvenile rheumatoid arthritis)**
- **Systemic lupus erythematosus (SLE)**
- **Vasculitis disorders, including:-**

➢ **PAN.**

➢ **Rheumatoid disease with vasculitis.**

➢ **Granulomatosis with polyangiitis (formerly known as Wegener’s granulomatosis)**

- **Polymyositis**
- **Bechet's disease**
- **Rheumatic fever (in regions where still endemic) .**

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❖ A etiology of pyrexia of unknown origin (PUO)

❑ Miscellaneous (~20%)

➢ Cardiovascular

- **Atrial myxoma, aortitis, aortic dissection**

➢ Respiratory

- **Sarcoidosis, pulmonary E. and other thromboembolic disease, extrinsic allergic alveolitis.**

➢ Gastrointestinal

- **Inflammatory bowel disease, granulomatous hepatitis, alcoholic liver disease, pancreatitis.**

➢ Endocrine/metabolic

- **Thyrotoxicosis, thyroiditis, hypothalamic lesions, pheochromocytoma, adrenal insufficiency, and hypertriglyceridemia.**

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❖ A etiology of pyrexia of unknown origin (PUO)

❑ Miscellaneous (~20%)

➢ Hematological

✓ Hemolytic anemia.

✓ Paroxysmal nocturnal hemoglobinuria.

✓ Thrombotic thrombocytopenic purpura.

✓ Myeloproliferative disorders.

✓ Castleman's disease.

✓ Graft-versus-host disease (after allogeneic hematopoietic stem cell transplantation).

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❖ A etiology of pyrexia of unknown origin (PUO)

❑ Miscellaneous (~20%)

- ➢ Inherited
  - ✓ Familial Mediterranean fever.
  - ✓ Periodic fever syndromes.

- ➢ Drug reactions
  - ✓ Antibiotic fever.
  - ✓ Drug hypersensitivity reactions.
  - ✓ Others.
- ➢ Factitious fever

❑ Idiopathic (~15%)

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❖ Clues to the diagnosis of factitious fever:-

A patient who looks well
Bizarre temperature chart with absence of diurnal variation and/or temperature-related changes in pulse rate
Temperature > 41°C
Absence of sweating during effervescence
Normal erythrocyte sedimentation rate and C-reactive protein despite high fever
Evidence of self-injection or self-harm
Normal temperature during supervised (observed) measurement
Infection with multiple commensal organisms (e.g. enteric or mouth flora

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❖ Investigations :-

- If initial investigation of fever is negative, further microbiological and non-microbiological investigations should be considered.
- The selection and prioritization of tests will be influenced by the geographical location of potential exposure to pathogens.
- Lesions identified on imaging should usually be biopsied for culture.
- Histopathology or NA detection, particularly in patients who have received prior antimicrobials,
- rRNA analysis may aid diagnosis if a microorganism is not cultured.

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❖ Investigations :-

- **Positron emission tomography (PET) scans may aid diagnosis of vasculitis or help selection of biopsy sites.**

- **Liver biopsy may be justified – for example, to identify idiopathic granulomatous hepatitis if there are biochemical or radiological abnormalities.**

- **Bone marrow biopsies have a diagnostic yield of up to 15%, most often revealing hematological malignancy, myelodysplasia or tuberculosis, and also identifying brucellosis, typhoid fever or visceral leishmaniasis.**

- **Bone marrow should be sent for culture, as well as microscopy.**

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❖ Investigations :-

- **Laparoscopy is occasionally undertaken with biopsy of abnormal tissues.**
- **Splenic aspiration in specialist centers is the diagnostic test of choice for suspected visceral leishmaniasis.**
- **Temporal artery biopsy should be considered in patients over the age of 50 years, even in the absence of physical signs or a raised ESR.**
- **‘Blind’ biopsy of other structures in the absence of localizing signs or laboratory or radiology results is unhelpful.**

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❖ **Investigations :-**

❑ **Microbiological investigation :-**

❑ **Location-independent investigations**

➢ **Microscopy**

- **Blood for atypical lymphocytes (EBV, CMV, HIV-1, hepatitis viruses or *Toxoplasma gondii*).**
- **Respiratory samples for mycobacteria and fungi.**
- **Stool for ova, cysts and parasites**
- **Biopsy for light microscopy (bacteria, mycobacteria, fungi).**
- **Urine for white or red blood cells and mycobacteria (early morning urine × 3).**

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❖ **Investigations :-**

❑ **Microbiological investigation :-**

❑ **Location-independent investigations**

➢ **Culture**

- **Aspirates and biopsies (e.g. joint, deep abscess, debrided tissues).**
- **Blood, including prolonged culture and special media conditions.**

- **Sputum for mycobacteria**
- **CSF**

- **Gastric aspirate for mycobacteria**
- **Stool**

- **Swabs**
- **Urine ± prostatic massage in older men.**

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Pyrexia of unknown origin

❖ **Investigations :-**

❑ **Microbiological investigation :-**

❑ **Location-independent investigations**

➢ **Antigen detection**

- **Blood, e.g. HIV antigen, cryptococcal antigen, Aspergillus galactomannan ELISA and for Aspergillus and other causes of invasive, fungal infection.**

- **CSF for cryptococcal antigen**

- **Bronchoalveolar lavage fluid for Aspergillus galactomannan**

- **Nasopharyngeal aspirate/throat swab for respiratory viruses, e.g. IAV or RSV**

- **Urine, e.g. for Legionella antigen.**

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❖ **Investigations :-**

❑ **Microbiological investigation :-**

❑ **Location-independent investigations**

➢ **Nucleic acid detection**

- **Blood for Bartonella spp. and viruses**
- **CSF for viruses and key bacteria (meningococcus, pneumococcus, Listeria monocytogenes)**

- **Nasopharyngeal aspirate/throat swab for respiratory viruses.**
- **Sputum for Mycobacterium tuberculosis (MTB).**

- **Bronchoalveolar lavage fluid, e.g. for respiratory viruses.**
- **Tissue specimens, e.g. for T. whipplei.**

- **Urine, e.g. for Chlamydia trachomatis, Neisseria gonorrhoeae.**
- **Stool, e.g. for norovirus, rotavirus.**

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❖ **Investigations :-**

❑ **Microbiological investigation :-**

❑ **Location-independent investigations**

➢ **Immunological tests**

- **Serology (antibody detection) for viruses, including HIV-1, and some bacteria.**

- **Interferon-gamma release assay for diagnosis of exposure to tuberculosis.**

Note this will not distinguish latent from active disease and can only be used to trigger of active disease) further investigations.

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❖ **Investigations :-**

❑ **Microbiological investigation :-**

❑ **Geographically restricted tests**

➢ **Microscopy**

- **Blood for trypanosomiasis, malaria and *Borrelia* spp.**
- **Stool for geographically restricted ova, cysts and parasites.**
- **Biopsy for light microscopy (dimorphic fungi, *Leishmania* spp. And other parasites).**
- **Urine for red blood cells and schistosome ova.**

➢ **Antigen detection**

- **Blood, e.g. dengue virus antigen, Histoplasma antigen and malaria antigen.**

Pyrexia of unknown origin

❖ **Investigations :-**

❑ **Microbiological investigation :-**

❑ **Geographically restricted tests**

➢ **Nucleic acid detection**

- **Blood for causes of viral hemorrhagic fever.**

- **CSF for geographically restricted viruses, e.g. Japanese encephalitis virus.**

- **Nasopharyngeal aspirate/throat swab or bronchoalveolar lavage fluid for geographically restricted respiratory viruses.**

➢ **Immunological tests**

- **Serology (antibody detection) for viruses, dimorphic fungi and protozoa.**

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❖ **Additional investigations in PUO :-**

❑ **Serological tests for connective tissue disorders:**

- **Autoantibody screen.**
- **Complement levels.**

- **Immunoglobulins.**
- **Cryoglobulins**

❑ **Ferritin.**

❑ **Echocardiography.**

❑ **Ultrasound of abdomen.**

❑ **CT/MRI of thorax, abdomen and/or brain.**

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❖ **Additional investigations in PUO :-**

❑ **Imaging of the skeletal system:.**

- ➢ **Plain X-rays.**
- ➢ **CT/MRI spine.**
- ➢ **Isotope bone scan.**

❑ **Labelled white cell scan.**

❑ **Positron emission tomography (PET)/single-photon emission computed tomography (SPECT)**

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❖ Additional investigations in PUO :-

❑ Biopsy:

- Bronchoscopy and lavage ± transbronchial biopsy.
- Lymph node aspirate or biopsy.

- Biopsy of radiological lesion.
- Biopsy of liver.

- Bone marrow aspirate and biopsy.
- Lumbar puncture.

- Laparoscopy and biopsy.
- Temporal artery biopsy.

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❖ Prognosis

- **No cause is found in approximately 10-15% of PUO cases.**
- **As long as there is no significant weight loss or signs of another disease.**
- **The long-term mortality is low .**

THANK YOU